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Enantioselectivity Determination

Direct Visual Detection of the Stereoselectivity of a Catalytic Reaction**

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The unique handedness of the essential molecules of life and the key role of homochirality in the development of new drugs[1] is a source of inspiration for numerous efforts to design efficient catalytic procedures to prepare single enantiomers of biologically active compounds.[2] The analysis of the enantioselectivity in the (high-throughput) screening of asymmetric catalysts[3] is often the rate-determining step,[3,4] despite the introduction of ingenious combinatorial methods[4–6] and miniaturization.[3,4] Thus, an instant read-out of the enantiomeric excess of a chiral product would be an important step forward.[7] Herein we report a color test for the rapid determination of the stereoselectivity of a catalytic conversion, which offers a simple solution to the fundamental challenge of directly visualizing the molecular chirality of a reaction product. The incorporation of a mesogenic unit into a typical substrate used in the screening of chiral catalysts allows the immediate assessment of the enantiomeric excess of the product from the color induced in a liquid-crystalline matrix.

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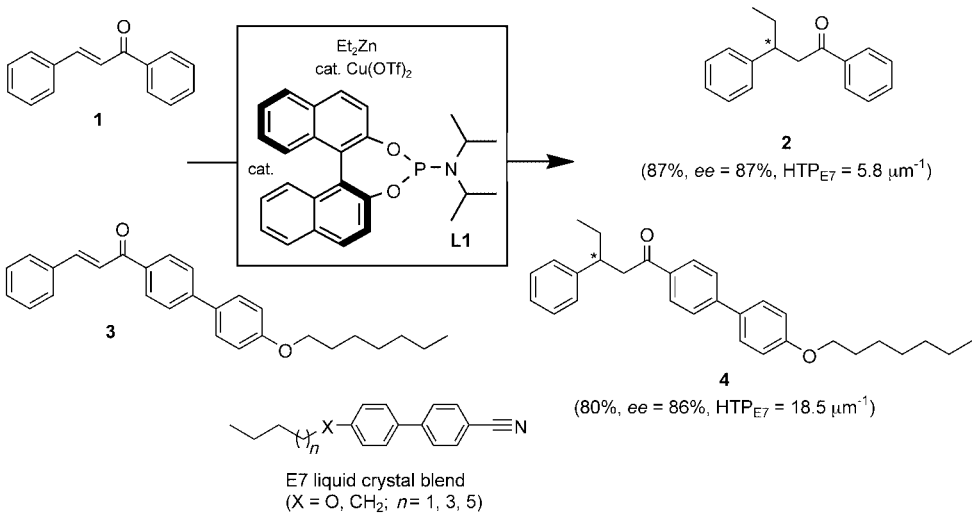
Our design is based on the principle of color generation in doped cholesteric liquid-crystalline (LC) films.[8] Cholesteric or twisted nematic liquid-crystalline phases can be induced by doping an achiral nematic liquid-crystalline host compound with a suitable chiral nonracemic guest molecule (the dopant).[9] Aligned films of these liquid-crystalline phases are known to reflect light of a particular wavelength. The wavelength can be tuned within the range of the visible spectrum (ca. 360–700 nm) by careful choice of the chiral dopant and leads to brightly colored liquid-crystalline films. The reflected wavelength is dependent on the pitch (p) and the refractive index (n) of the material as well as on the incident angle (α) of the light. The pitch, in turn, is inversely proportional to the concentration (c), the helical twisting power (β), and, most importantly for the present application, the enantiomeric excess (*ee*) of the chiral guest molecule. The wavelength of reflection is directly related to the enantiomeric excess according to Equation (1).[9]

$$\lambda(\alpha) = n\,p\cos[\sin^{-1}(\sin\alpha/n)] = n\,(\beta\,c\,ee)^{-1}\cos[\sin^{-1}(\sin\alpha/n)] \qquad (1)$$

The helical twisting power, which is an intrinsic property of any chiral dopant, is a measure of the efficiency of the molecule to cause helical induction in a liquid-crystalline matrix. In general, the magnitude of the helical twisting power of typical products of enantioselective catalytic transformations is too small to obtain colored liquid-crystalline phases, since there is a limit to the dopant concentration in a liquid-crystalline host. To overcome this problem we envisioned that a reaction product with high structural resemblance to the liquid-crystalline host should give rise to both a higher helical twisting power and an improved compatibility. Recently, we reported a method based on this principle, which allowed the evaluation of the enantiomeric excess of chiral products by simple inspection of the color after a derivatization step.[10,11] The major drawback of this method, particularly when performing multiple parallel reactions, is the essential, but time-consuming, derivatization step.

The common practice for initial screening of new effective catalysts involves conversion of benchmark reagents, thus we reasoned that a simple redesign of such substrates to incorporate a mesogenic unit would result in an immediate color test to assess the stereochemical outcome of a particular catalytic conversion. In other words, when the product of the enantioselective catalysis itself structurally resembles the liquid-crystalline host the enantiomeric excess can be determined directly after doping, without the need for any derivatization. To demonstrate this concept we chose the copper-catalyzed asymmetric conjugate addition of diethylzinc to chalcone as a model reaction, as this is a well-described and extensively studied C–C bond-formation reaction (Scheme 1).[12–15]



Scheme 1. Copper-catalyzed asymmetric conjugate addition of diethylzinc to chalcone (**1**) and *para-n*-heptyloxyphenyl-substituted chalcone **3**. Tf = trifluoromethanesulfonyl.

The ethyl adduct **2** of the benchmark reagent chalcone **1** shows no structural resemblance to the liquid-crystalline host E7 and results in a low helical twisting power of 5.8 μm^{-1}.[16] It is, therefore, not possible to generate a colored liquid-crystalline film using E7 doped with **2**. To realize a structural resemblance between the asymmetric conjugate addition product and E7 we employed *para-n*-heptyloxyphenyl-substituted chalcone **3** (see Supporting Information) as a starting material instead of chalcone (**1**). A prominent structural motif both in the LC host material E7 and chiral product **4** is the *para*-alkoxy-substituted biphenyl mesogenic unit. This feature resulted in a significantly higher helical twisting power of 18.5 μm^{-1} for **4**, thus allowing color generation in liquid-crystalline films aligned on a polyimide-coated glass plate. In accordance with Equation (1), doping of achiral E7 with 21 wt% of enantiomerically pure **4** resulted in a violet-blue liquid-crystalline film. Samples of E7 doped with **4** with 100, 90, 80, 70, 60, and 50% *ee* (prepared by mixing enantiomerically pure and racemic **4**) afforded liquid-crystalline phases with colors ranging from violet-blue (100% *ee*) to deep red (50% *ee*), thus allowing direct visual determination of the enantiomeric excess of the chiral dopant (Figure 1). The enantiomeric excess of the product can further be quantified by measuring the exact wavelength of reflection with high accuracy, since a change in the *ee* value of only 1% results in a readily detectable shift of at least 4.0 nm in the wavelength of maximum reflection. A calibration curve for the determination of the enantiomeric excess was obtained during the spectroscopic measurement of the reflection wavelength of

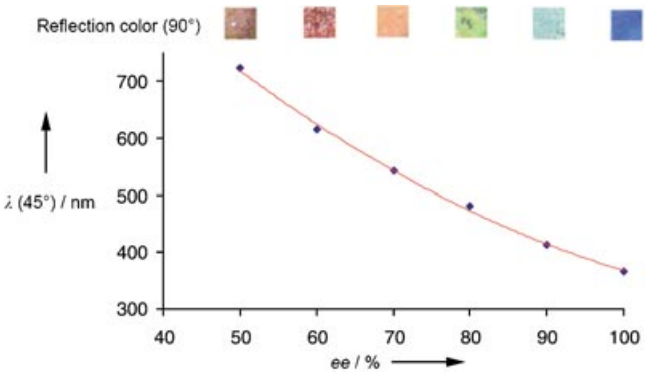


Figure 1. Color (90°) and wavelength (λ(45°)) of the reflection of E7 doped with 21 wt% of **4** with different *ee* values. The depicted colors are photographs of the LC samples taken perpendicular (90°) to the surface of the film. The wavelengths of maximum reflection were measured at an incident light angle of 45°.

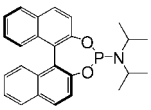
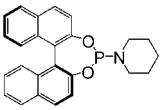
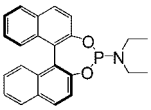
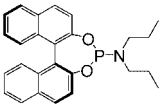
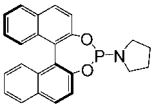
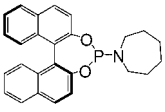
the colored phases described above (at an incident angle of 45°; Figure 1).

For compound **3** to be applicable as a benchmark reagent for enantioselective conjugate additions it is essential that yields and enantioselectivities are comparable to those of **1**, the typical substrate for these reactions. Compound **3** was tested as a substrate in the catalytic conjugate addition of diethylzinc using $Cu(OTf)_2$ and ligand L1. It was rewarding to observe similar yields and enantioselectivities to those obtained for chalcone **1** (Scheme 1). The only difference was that compound **3** showed low solubility in toluene (the common solvent for these reactions) at −25 °C,[13] and therefore the reactions on this substrate were performed in dichloromethane. However, the change in solvent had only a minor influence on the yield and the enantioselectivity of the reaction.

To examine whether it is possible to measure the enantioselectivity of a conjugate addition reaction directly by applying the method and substrate described above, six chiral phosphoramidite ligands were tested (Table 1). This class of ligands is widely applied in conjugate additions to effect C–C bond formation.[13,15] The reactions were performed under standard conditions, and after quenching the reaction mixture and a simple filtration to remove the zinc and copper salts (as described in the Experimental Section) 21 wt% mixtures of the product and liquid-crystalline host E7 were applied to linearly rubbed, polyimide-coated glass plates to generate colored liquid-crystalline films (Table 1). Comparison of the colors of these films to those of films of E7 doped with **4** with various known *ee* values allows quantification of the enantioselectivity of the reaction by visual inspection (Figure 1). It was possible to accurately assess the enantiomeric excess of product **4** by measuring the reflection wavelength and using the calibration curve depicted in Figure 1. To ascertain the accuracy of our new technique the *ee* values obtained from the color test were compared to those determined by HPLC on a chiral stationary phase. An excellent correlation was found in all cases, especially between the values obtained by reflection wavelength measurements and HPLC. The values obtained by visual inspection are less precise, although a difference in an *ee* value of $\leq 5\%$ can readily be detected by the naked eye. The possibility of visual inspection offers the advantage of instant read-out of the enantiomeric excess, which is ideal for screening purposes in combinatorial catalysis. Full conversion into the desired product was always achieved in these reactions; however, this color test can still be applied even if full conversion is not reached, since in this case the observed color can act as a measure of the combination of conversion and *ee* value [Eq. (1)].[17]

These results clearly demonstrate that it is possible to determine the enantiomeric excess of the product of a catalytic asymmetric reaction by a liquid-crystalline-based color test, as illustrated for a key carbon–carbon bond-forming reaction. In the 1,4-addition of diethylzinc to **3**, product **4** was obtained with yields and enantioselectivities similar to the ethyl adduct of chalcone, which is a common

Table 1: Screening results of chiral catalysts;[a] comparison of methods for the determination of *ee* values.

Ligand	Ligand structure	Color	*ee* (reflection wavelength) [%]	*ee* (HPLC) [%]
L1			86	86
L2			71	72
L3			60	59
L4			66	64
L5			60	58
L6			71	74

[a] Ligands were tested in the reaction with **3** in Scheme 1. See Experimental Section for details.

substrate in catalytic reactions leading to C–C bond formation. These results make substrate **3** a valuable benchmark reagent for these reactions. Enantioselectivities can be determined visually (by looking at the color of an aligned liquid-crystalline film doped with the product) or spectroscopically (by measuring the reflection wavelength and comparing it with a calibration curve). Both methods, although of different accuracy, give *ee* values comparable to results obtained by HPLC on a chiral stationary phase. This new procedure involves simple filtration and mixing, and does not require chiral auxiliaries or post-reaction derivatization. Furthermore, microgram quantities of product are sufficient. In conclusion, this methodology allows fast and accurate screening of enantioselectivities in asymmetric catalysis, and the development of simple color tests for a wide range of asymmetric transformations is envisioned based on this principle.

Experimental Section

General procedure: A chiral ligand (L1–L6, 15.0 μmol, 10 mol%), $Cu(OTf)_2$ (2.7 mg, 7.5 μmol, 5 mol%), and dichloromethane (4.2 mL) were added to a flame-dried Schlenk flask under argon. The mixture was stirred for 1 h at room temperature, and then substrate **3** (60.0 mg, 0.15 mmol) was added. This mixture was stirred for an additional 15 min and subsequently cooled to −25 °C. Et_2Zn (0.35 mL, 1.0 M solution in hexanes) was added and the mixture was stirred for 2 days at −25 °C. The reaction was then quenched by the addition of saturated aqueous NH_4Cl (1 mL). The resulting mixture was dissolved in dichloromethane (50 mL) and filtered through a 3-cm plug of SiO_2 and collected in a flask of known weight. After evaporation of the solvent, the flask was weighed to determine the yield of the product (typically around 54 mg). The product was dissolved in toluene (5.0 mL) and an appropriate amount of this solution containing 0.80 mg of product was mixed with 85.7 μL of a stock solution of E7 in toluene (17.55 mg in 500 μL). The solution was then poured onto a linearly rubbed, polyimide-coated glass plate. The color appeared immediately after evaporation of the toluene in the air at room temperature. These phases were stable for 1–3 days, depending on the cholesteric pitch. The colors of these phases could be detected by visual inspection or by measuring the reflection wavelength at a 45° angle by using a modified UV apparatus.

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Keywords: asymmetric catalysis · chirality · combinatorial chemistry · enantioselectivity · liquid crystals

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[17] A colored LC phase can be obtained, in theory, from any reaction mixture for **4** (% *ee* × % conversion) ≥ 5000 [Eq. (1)]. However, at this point no discrimination between the *ee* value and conversion can be made, but as a good chiral catalyst should give high conversion as well as high enantioselectivity this method can be applied in the screening of both quantities at the same time.

